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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,077	11/24/2003	Anthony F. Barbet	UF-167XC3D2	8724

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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 11/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/722,077	BARBET ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-16* is/are pending in the application.

4a) Of the above claim(s) *8-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2004*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application

6)☒ Other: Sequence attachments (10 pages

DETAILED ACTION

The response and amendment filed 8-9-06 has been entered into the record. Claim 7 has been canceled. Claims 1-6 and 8-16 are pending.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application 60/130,725, 4-11-999 upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-6 and 15-16 of this application. The claimed nucleic acid sequences were not disclosed in the provisional application.

It is noted that this application claims priority under 35 U.S.C. 120 to prior Application Nos. 09/337,827; 08/953,326; and 08/733,230. It is noted that none of these prior applications provide written description of the instantly claimed nucleic acid sequence (SEQ ID NO:25) encoding the major antigenic protein-2 (MAP2; SEQ ID NO:26) from *Cowdria ruminatium*. As such, the filing date for prior art purposes is that of parent Application No. 09/553,662, filed April 21, 2000.

The current status of all nonprovisional parent applications referenced should be included. It is noted that the current status of 09/337,827 is not updated as abandoned.

Drawings

The drawings in this application have been accepted. No further action by Applicant is required.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify the citizenship of each inventor (i.e. Ganta, Burridge, Mahan and Alleman).

Information Disclosure Statement

The information disclosure statement filed 4-6-2004 has been considered. An initialed copy is enclosed.

Election/Restrictions

Applicant's election of Group I (claims 1-6 and new claims 15 and 16) in the response filed 8-6-06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 8-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-3, 15 and 16 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claimed invention is drawn to a composition comprising a nucleic acid encoding protein product of nature. Products of nature are not patentable because they do not reflect the "hand of man" in the production of the product or manufacturing process. *Diamond v. Chakrabarty,* 206 USPQ 193 (1980). Additionally, purity of naturally occurring product does not necessarily impart patentability. *Ex parte Siddiqui* 156 USPQ 426 (1966). However when purity results in new utility, patentability is considered. *Merck Co. V. Chase Chemical Co.* 273 F. Supp 68 (1967). See also American *Wood v. Fiber Disintergrating Co.*, 90 US 566 (1974); *American Fruit Growers v. Brogdex Co.* 283 US 1 (1931); *Funk Brothers Seed Co. V. Kalo Innoculant Co.* 33 US 127 (1948). Filing of arguments and evidence of a new utility imparted by the increased purity of the claimed invention *and amendment to the claims to recite the essential purity* of the claimed products in the composition is suggested to obviate this rejection. For example, "An isolated nucleic acid...".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims recite nucleic acid encoding immunogenic fragments that are protective against disease or death caused by a rickettisal pathogen. The specification discloses that the mature polypeptide (residues 46-618) provides for reduced mortality in a homologous challenge model with the identical organism (*Cowdria ruminatium*) from which the gene was derived. The mature polypeptide is not a fragment because the protein only exists in nature as the mature form as the "signal peptide" is cleaved from the protein during its synthesis process. As such, the claims encompass numerous fragments that are potentially immunogenic, however the specification does not disclose any fragments that provide for the claimed function of protective against disease or death caused by rickettisal pathogens in general (i.e. other species of *Cowdria*, *Rickettsia* spp. *Ehriichia* spp. *Anaplasma* spp). The specification does not describe a number of fragments that are both immunogenic and protective as claimed. The scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Although the specification teaches that variants can be readily screened, the specification and the claim do not provide any guidance on the structure of the polypeptide and what changes can or can not be made. Structural features that could distinguish compounds in the genus from others

in the protein class are missing from the disclosure and the claims. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general guidance is needed. Since the disclosure fails to describe the common attributes or structural characteristics that identify members of the genus, and because the genus is highly variant, the functions of immunogenic and protective alone is insufficient to describe the genus of fragments of the polypeptide of that function equivalently. One of skill in the art would reasonable conclude that the disclosure of a single SEQ ID NO, fails to provide a representative number of species of fragments to describe the claimed functional genus. Applicants were not in possession of the claimed genus because the specification does not convey to one of skill in the art a representative number of functional fragments that have the claimed structure and function. The genus of fragments with the claimed function is substantial and highly variant because the polypeptides do not appear to have a common structure and function. The recitation of "fragment" does not convey a common structure nor a common function. As such, generic fragments that are unrelated via structure and function are highly variant and not conveyed by way of written description by the specification at the time of filing. As such the specification lacks written description for the genus of immunogenic fragments that are protective. The specification fails to provide specific representation of fragments that are immunogenic and protective and therefore, one skilled in the art would not recognize that applicants had possession of the genus of immunogenic fragments for use in protection from infection as recited in the intended use as claimed.

Claims 1-6, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid encoding the polypeptide as set forth in SEQ ID NO:26 or an isolated nucleic acid encoding the mature polypeptide as set forth in residues 16-205 of SEQ ID NO:16, nucleic acid vaccine vectors and

compositions comprising such in order to provide for a reduced mortality from the pathogen *Cowdria ruminatium* it does not reasonably provide enablement for the genus of protective immunogenic fragments and protection for any rickettsial pathogen including other *Cowrida* spp, *Rickettsia* spp. *Ehriichia* spp and *Anaplasma* spp; protection from infection or protection from death. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to a polynucleotide encoding a polypeptide having the characteristic of electing an immune response protective against disease or death caused by a rickettsial pathogen. The term rickettsial pathogen includes but is not limited to Genera and species other than *Cowdria ruminatium.* These organisms are other *Cowrida* spp. and species from the genera *Rickettsia, Ehrlichia* and *Anaplasma.* SEQ ID NO:26 encoded by the nucleic acid sequence set forth in SEQ ID NO:25 is identified as MAP2 from *Cowdria ruminatium.* The teachings of the specification indicate that a modest increased 32% survival rate when an animal vaccinated with a nucleic acid vaccine vector comprising residues 16-205 of SEQ ID NO:1, when challenged with the same organism from which the nucleic acid was derived (i.e. homologous). The specification as filed does not provide evidence of heterologous immune protection against disease or death caused by any rickettsial pathogen as broadly contemplated and claimed.

One of skill in the art would have reason to doubt the asserted truth of the teachings of the specification for cross-protective immunity because the rickettsial art specifically teaches that prior infection does not protect against homologous strains or heterologous strains depending on the particular rickettsial pathogen. For example, Ehrlichia (see abstracts, Breitschwerdt et al., Antimicrobial Agents and Chemotherapy, 42(2):362-368, Feb 1998; of record on 1449 Lewis et al, American Journal of Veterinary Research, 36(1):85-88, 1975; of Record on 1449) does not protect from homologous or heterologous spp and strains and that vaccine failure results from heterogeneity of

isolates (see abstracts, Dutta et al., Journal of Clinical Microbiology, 36(2):506-512, 1998 of record on 1449 and Vemulapalli et al., Journal of Clinical Microbiology, 33(11):2987-2993, 1995 of record on 1449). Homologous variation of the art encompasses the instant immunogenic fragments encoded by homologous genes. Mere similarity in structure cannot predict protection. Both the specification and the art fail to demonstrate that the proteins of SEQ ID NO:25 or 26 have the ability to generate an immune response in a susceptible host animal and that the immune response so generated is sufficient to protect against disease and death against infection with a heterologous rickettsial organism as instantly claimed. As a result one skilled in this art would have reason to doubt that the nucleic acids which encode these proteins would likewise be effective as claimed. Applicants' have not demonstrated that either the claimed protein or the nucleic acid encoded by the protein or any fragment thereof generate the immune responses which have been demonstrated for other nucleic acid vaccines which are protective (i.e. cytotoxic T-lymphocyte, T-helper and antibodies). None of the biological hallmarks demonstrating either protein or nucleic acids encoding the protein for vaccination have been demonstrated in this application. Consequently, reduced mortality evidenced by SEQ ID NO:25, of the MAP2 gene of *Cowdria ruminatium* would not be readily appreciated by the artisan skilled in rickettsial diseases to provide for cross-protective immunity to other species of *Cowdria* and species from the genera of *Rickettsia, Ehrlichia* and *Anaplasma*. The life cycle of rickettsial organisms is highly complex. The organisms are well known to be able to establish chronic infection by antigenic variation and that the variation presented in the life cycle in the host animal may not represent the antigens present in the tick vector. As a result, immunizing with nucleic acids encoding the singe protein in the host animal life cycle would not be expected to protect an animal from death or infection because the specification fails to teach that the proteins are present in the tick vector. Unless the antigen of interest is expressed in the tick, protection from disease and death cannot occur by means of vaccination. In the absence of this critical

information in the specification and in the absence of any evidence demonstrating the protection from disease and death by the instantly claimed nucleic acids or immunogenic fragments thereof, the specification is not enabled. Vaccination with an antigen that is variant during the host life cycle would not be expected to protect from disease or death due to the well established principle of antigenic variation in the life cycle of rickettsial pathogens as evidenced above by the *Ehrlichia* sp which allows for chronic infection in the susceptible host. The specification fails to teach that the claimed nucleic acids encoding a protein antigen is present in the tick salivary gland and are expressed regardless of the variant types expressed in the blood of the infected animals (see abstract, Rurangirwa et al, Proceedings of the National Academy of Sciences, 96(6):3171-3176, 1999; of record in 1449). In view of the complex life cycle of rickettsial pathogens, one skilled in the art would have reason to doubt the validity and functionality of applicants assertions that the recited nucleic acids or immunogenic fragments thereof are protective as claimed. The specification fails to describe a genus of protective immunogenic fragments, does not identify the protective epitopes within SEQ ID NO:26, the mature protein is not considered by the art to be a "fragment", because it is the only form present in the cells because the signal or leader sequence is cleave during protein production. As such, the specification lacks written description of immunogenic fragments that are protective as instantly claimed.

In the absence of further guidance from applicants and in view of the complex life cycles of the richettsial pathogens, the use of antigenic variation to escape the host animals immune system, the lack of teaching for protection of either the protein in the art or the nucleic acid in the specification, the lack of specific characterization of MAP2 proteins and nucleic acid in the life cycle of the rickettsial sp. by the specification, the unpredictability in the art with respect to protection of homologous and heterologous species, the lack of protection with homologous and heterologous which establishes that sequence similarity is not predictive of protection from disease and death as alleged, it

would require undue experimentation on the part of the skilled artisan to make use the instantly claimed invention.

Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 recites that said polynucleotide encodes amino acids 16-205 as depending from claim 15. It is noted that "encoding" language is viewed as open and as such, this claim does not appear to further limit the subject matter in claim 15. Do applicants intend closed language, consisting of ? If closed language is desired, it is suggested that Applicants amend the language to recite that "The composition according to claim 15, wherein the polynucleotide encodes the polypeptide consisting of residues 16-205 as set forth in SEQ ID NO:26.

Claim Rejections - 35 USC § 102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the

subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 3, 5, 6, 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Mahan et al, (Microbiology, 140(8):2135-2142, 1994).

As to claims 1-3, 6, 15 and 16, Mahan et al teach a the molecular cloning of a gene encoding the immunogenic 21 kDa protein of *Cowdria ruminatium* , the pathogenic agent that causes heartwater. The nucleic acid of ORF 1 encodes a 21 kDa protein that was immunogenic and reacted to all sera tested from heartwater-infected animals (see abstract page 2138, Figure 2). The cloned DNA was subcloned into a pFLAG expression vector for high level expression in *E. coli* (page 2140, column 1). Mahan et al teach the mature protein of ORF-1 that is generated by the cleavage after the N-terminal signal peptide (see Figure 2, page 2138; page 2139, column 1), as such Mahan et al teaches a fragment of SEQ ID NO:26 that is immunogenic. It is noted that the polypeptide of ORF1 is 100% identical as compared with SEQ ID NO:26 as recited in the claims and that the corresponding nucleic acid of SEQ ID NO:25 is 100% identical as depicted in the Figure.

Residues 20-209 of the mature protein of ORF1 is 100% identical as compared to residues 16-205 of SEQ ID NO:26 (see attached alignment of SEQ ID NO:25 with the sequence of Mahan et al). Mahan et al teach the isolated *C. ruminatium* DNA in 70% (v/v) ethanol (page 2136, column 2, first full paragraph) and since ethanol is a pharmaceutically acceptable carrier, Mahan et al is seen to provide for the claimed composition of 5.

Claims 1, 2, 3, 5, 6, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mahan et al, Microbiology, 140(8):2135-2142, 1994 in view of Bowie et al (Clinical and Diagnostic Laboratory Immunology, 6(2):209-215, March 1999).

Mahan et al is set forth *supra*. Mahan et al differs in the length of the N-terminal signal peptide of 19-20.

Bowie et al teaches that there is a predicted ribosomal binding site 5' to the second methionine but 3' to the first methionine (Figure 3). Thus, it appears that the reported amino acid sequence of MAP2 (17) maybe incorrect and should actually be shorter by 4 amino acids at the N-terminus.

It would have been *prima facie* obvious to the skilled artisan at the time that the invention was filed that the MAP2 protein of *Cowdria ruminatium* was actually shorter by 4 amino acids.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sedegah et al (PNAS, 91:9866-9870, 1994) in view of Mahan et al (Microbiology, 140(8):2135-2142, 1994) and Bowie et al (Clinical and Diagnostic Laboratory Immunology, 6(2):209-215, March 1999).

Sedegah et al teach the immunization of animals using parasite nucleic acid encoding a circumsporozoite protein. Sedegah et al teach construction of a vector plasmid suitable for injection and the vector suspended in a sterile phosphate buffered saline (see page 9867, column 1, lines 3-7). Sedegah et al teach that the parasite plasmid DNA was

effective to induce an immune response in an animal (see page 9867, column 2, Table 1). Sedegah et al differs by not teaching the rickettsial DNA comprising SEQ ID NO:25 or mature fragments thereof). Sedegah et al teach that the utility of plasmid DNA immunization against a non-viral infection and by obviating the requirement for peptide synthesis, expression and purification of recombinant proteins, and adjuvants, this method of immunization provides an important alternative for rapid identification of protective B- and T-cell epitopes (see abstract page 9866).

Mahan et al is set forth *supra*.

Bowie et al is set forth *supra*. In addition, Bowie et al teach that analysis of MAP2 and its homologs revealed that the whole protein lacks specificity for heartwater diagnosis. The development of epitope-specific assays using this sequence information may produce diagnostic tests suitable for C. ruminatium and also for other related rickettsiae.

It would have been prima facie obvious to substitute the nucleic acid of encoding the ORF1 of Mahan et al or MAP2 of Bowie or immunogenic fragments of either for the circumsporozoite open reading frame in the immunizing plasmid of Sedegah et al because Sedegah et al teach that ORF1 of he utility of plasmid DNA immunization against a non-viral infection and by obviating the requirement for peptide synthesis, expression and purification of recombinant proteins, and adjuvants, this method of immunization provides an important alternative for rapid identification of protective B- and T-cell epitopes and Mahan et al and Bowie et al teach the utility of the polypeptide or epitopic fragments thereof for the serological diagnosis of heartwater.

Status of the Claims

Claims

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Acting Supervisory Examiner Mark Navarro can be reached on 571-272-0861.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy, Ph.D.
Primary Examiner
Art Unit 1645